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ning of each regular issue of the PCT Gazette.*

(54) Title: ACE-INHIBITORS HAVING ANTIOXIDANT AND NITRICOXID-DONOR ACTIVITY

(57) Abstract: Multifunctional ACE inhibitor compounds are provided, that combine ACE-inhibiting activity with capability to scavenge superoxide and other reactive oxygen species, and that may further function as nitric oxide donors. The compounds are useful for preventing or treating various disorders, including cardiovascular, and diabetes associated disorders.



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# INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/IL 03/01006

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/385 A61K31/40 A61K31/401 A61K31/403 A61K31/445  
C07D403/12 C07D207/08 C07D409/12 C07K5/06 C07D209/44  
C07D409/06 A61P9/00 A61P9/04 A61P09/06 A61P09/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/34303 A (UNIV BOSTON ;VITA JOSEPH A (US); WORCEL MANUEL (US); LOSCALZO JOSE) 2 May 2002 (2002-05-02) page 3, line 7 - line 15 page 13, line 17 - line 22 page 14, line 15 - page 15, line 8 page 24, line 10 page 25 - page 28, line 19 claims 20,22,58,87,89,101 -----	1-48
X	WO 98/21193 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 22 May 1998 (1998-05-22) page 13, paragraph 3 page 18 - page 20; example 2 ----- -/--	1-48

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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# INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/61541 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) page 7, last paragraph page 38, last paragraph page 45, paragraph 4 claims 1,5 -----	1-48
X	US 5 025 001 A (LOSCALZO JOSEPH ET AL) 18 June 1991 (1991-06-18) column 8 - column 14 column 27 - column 31; examples 1-8 -----	1-48
A	WO 98/42661 A (YISSUM RES DEV CO ;HAJ YEHIA ABDULLAH (IL)) 1 October 1998 (1998-10-01) page 5, paragraph 3 page 8 - page 26 -----	1-48
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X	IWANAGA YOSHITAKA ET AL: "A nitric oxide-releasing derivative of enalapril, NCX 899, prevents progressive LV dysfunction and improves remodeling in cardiomyopathic hamsters with heart failure." CIRCULATION, vol. 106, no. 19 Supplement, 5 November 2002 (2002-11-05), pages II-510, XP009029725 Abstracts from Scientific Sessions;Chicago, IL, USA; November 17-20, 2002 ISSN: 0009-7322 (ISSN print) abstract -----	1-48

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# INTERNATIONAL SEARCH REPORT

Int... Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>VAN DER GIET M ET AL: "Captopril and quinapril reduce reactive oxygen species." EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, vol. 32, no. 10, October 2002 (2002-10), pages 732-737, XP002277635 ISSN: 0014-2972 page 733, column 2, last paragraph page 734; figure 1 page 735, column 1, last paragraph</p>	<p>1,3,5, 9-12,16, 17, 20-27, 29-31, 36,42-48</p>
X	<p>----- DJORDJEVIC V B ET AL: "CHANGES OF LIPID PEROXIDES AND ANTIOXIDATIVE FACTORS LEVELS IN BLOOD OF PATIENTS TREATED WITH ACE INHIBITORS" CLINICAL NEPHROLOGY, DUSTRI VERLAG, NUENCHEN-DEISENHOFEN, DE, vol. 47, no. 4, April 1997 (1997-04), pages 243-247, XP001104974 ISSN: 0301-0430 abstract page 245 - page 246, paragraph 1</p>	<p>1,3,5, 9-12,16, 17, 20-27, 29-31, 36,42-48</p>
X	<p>----- ARUOMA O I ET AL: "EVALUATION OF THE ABILITY OF THE ANGIOTENSIN-CONVERTING ENZYME INHIBITOR CAPTOPRIL TO SCAVENGE REACTIVE OXYGEN SPECIES" CHEMICO-BIOLOGICAL INTERACTIONS, vol. 77, no. 3, 1991, pages 303-314, XP002277636 ISSN: 0009-2797 page 307 - page 310, paragraph 1</p>	<p>1,3,5, 9-12,16, 17, 20-27, 29-31, 36,42-48</p>

# INTERNATIONAL SEARCH REPORT

ational application No.  
PCT/IL 03/01006

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-11, 20-35, 44-48 (all in part); 12, 36

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-11, 20-35, 44-48 (all in part); 12, 36

use of compounds comprising an ACE inhibitor component derived from a commercially available ACE inhibitor as defined in claim 12 a ROS scavenger component and optionally a NO donor component for the treatment of conditions as defined in claim 10.

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2. claims: 1-11, 18-35, 44-48 (all in part); 13, 14, 37-39

use of compounds comprising an ACE inhibitor component comprising a heterocycle as defined in claims 13 and 14 for the treatment of conditions as defined in claim 10.

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3. claims: 1-11, 18-35, 44-48 (all in part); 15, 40, 41

use of compounds comprising an ACE inhibitor component comprising a heterocycle as defined in claims 15 for the treatment of conditions as defined in claim 10.

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4. claims: 1-11, 18-35, 44-48 (all in part); 16, 17, 42, 43

use of compounds comprising an ACE inhibitor component according to formula IV as defined in claim 17 (compounds falling under the scope of claim 12 being excluded) for the treatment of conditions as defined in claim 10.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte Application No

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Int. Application No

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